EXHIBIT 2

IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF WEST VIRGINIA
CHARLESTON DIVISION

IN RE: ETHICON, INC.,
PELVIC REPAIR SYSTEM
PRODUCTS LIABILITY LITIGATION

MDL No. 2327

THIS DOCUMENT RELATES TO ALL
WAVE ONE CASES INVOLVING THE PROSIMA
PRODUCT

RULE 26 EXPERT REPORT OF BOB SHULL, M.D.

The following report is provided pursuant to Rule 26 of the Federal Rules of Civil Procedure. The opinions which are held and expressed are as follows:

I. QUALIFICATIONS

I am Dr. Bob Shull. My Curriculum Vitae (attached as **Exhibit A**) reflects my training, background, and publications. I graduated from Tulane Medical School and completed my residency training in Obstetrics and Gynecology at the University of Virginia in Charlottesville.

Throughout my career, I have had an interest in pelvic floor disorders of women, including pelvic organ prolapse and stress urinary incontinence. I have published original work in scientific journals regarding the evaluation and surgical management of these disorders.

Currently, I am Professor in the Division of Gynecology and member of the Section of Female Pelvic Medicine and Reconstructive Pelvic Surgery at the Scott and White Memorial Clinic and Hospital, Texas A&M System Health Science Center College of Medicine, in Temple, Texas. In this role, I maintain an active patient practice, supervise and teach medical students, residents, and fellows, and participate in clinical and basic science research. I also teach and lecture throughout the United States and in other parts of the world, often leading "hands-on" surgical workshops for colleague physicians.

I have significant experience with pelvic repair surgery of all types. I have performed many pelvic surgeries for both incontinence and/or prolapse. I have lectured nationally and internationally regarding these surgeries, outcomes, and complications. I have personally examined, diagnosed and treated approximately one hundred patients with mesh complications and removed some mesh from at least 70 women. I am familiar with the Prosima kit specifically,

as well as mesh products generally. I have also published articles in peer-reviewed journals relating to complications of synthetic mesh devices for prolapse repair.[1]

In formulating my opinions and preparing this report, I relied on my experience, the scientific literature, and corporate documents from the files of Ethicon, Inc. ("Ethicon"). The corporate documents were supplied to me by counsel.

II. SUMMARY OF OPINIONS

The following summarize my opinions in this case:

1. At the time of its introduction, there was insufficient scientific evidence supporting the implantation of the Prosima devices for pelvic organ prolapse.[2]

2. The Prosima devices (and similar prolapse mesh "kits") represented a significant departure from traditional surgical procedures performed for pelvic organ prolapse. Prosima devices offer no advantage over traditional repair.

3. The vagina is a different environment from the abdominal wall. Maintenance of vaginal compliance and distensibility is essential for bowel, bladder, and sexual function.

4. Insertion of a device containing polypropylene mesh "straps" presents specific risks and is inconsistent with sound pelvic reconstructive surgical principles.

5. There were no studies prior to introduction of the Prosima device demonstrating safety and efficacy of the Vaginal Support Device – Balloon Assembly. The predicate product for vaginal support device, the Silimed vaginal stent, had been cleared by the FDA in the summer of 1998 with the following indication for use: "designed to maintain the vaginal canal following radiological treatment or surgical procedures to restore, enlarge or create a vagina."[3]

6. Traditional surgical repairs are effective. The medical literature does not show improved outcomes with the use of the Prosima device or any other transvaginally placed mesh.

7. Mesh is associated with severe, life-changing complications that are not seen with traditional pelvic reconstructive surgery and are often difficult to treat.

8. Mesh removal surgery is complex and requires special expertise. Removal may not alleviate the patient's symptoms and may, in fact, make the symptoms worse.

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[1] e.g. Huffaker, Shull, and Thomas, A serious complication following placement of posterior Prolift, Int Urogynecol J (2009) 20:1383–1385; Brubaker and Shull, A perfect storm, In t Urogynecol J (2012) 23:3-4.
[2] Carey, M., P. Higgs, J. Goh, J. Lim, A. Leong, H. Krause, and A. Cornish. "Vaginal Repair with Mesh Versus Colporrhaphy for Prolapse: A Randomised Controlled Trial." BJOG 116, no. 10 (Sep 2009): 1380-6.
[3] Silimed 510k.

9. The characteristics of polypropylene mesh when implanted vaginally for pelvic organ prolapse include chronic inflammation, foreign body reaction, fibrosis and scarring, nerve entrapment, deformation, stiffening, shrinkage and contraction, and degradation, all of which have clinical significance.

10. Ethicon did not provide doctors and patients with complete and accurate information regarding the efficacy, safety, and complications associated with the Prosima devices and their management.

11. Ethicon failed to disclose the lack of benefit of pelvic organ prolapse surgery using the Prosima device to physicians and patients.

12. There were no scientific clinical trials demonstrating safety of the Prosima device before its introduction into the commercial market.

13. Ethicon should have anticipated the serious and permanent complications that are caused by the Prosima mesh kit.

14. From a clinical perspective, Ethicon did not exercise due diligence in the design and development of the Prosima mesh.

15. Ethicon lacked scientific rigor in the testing and reporting of its pelvic floor products including the use of Gynemesh.

16. Ethicon did not heed the warnings from the hernia and gynecologic literature regarding the use of polypropylene mesh.

17. If Ethicon had properly tested its products, certain problems and complications would have been identified before they were used in a clinical setting.

18. Ethicon inappropriately marketed its prolapse mesh products to all physicians and did not properly train these physicians in the unique aspects of patient selection and patient counseling of long-term sequelae of mesh kits.

19. After the products were used in general clinical setting, Ethicon did not systematically monitor their products for safety or efficacy or evaluate physician feedback.

20. The problems associated with the Prosima device are inherent in the concept and design and occur even when the device is placed properly. As an example of significant adverse events please refer to the case report by Hong describing massive internal bleeding associated with the Prosima and Gynemesh device.[4]

[4] Hong, M. K., C. Y. Liao, T. Y. Chu, P. C. Chen, and D. C. Ding. "Internal Pudendal Artery Injury During Prolapse Surgery Using Nonanchored Mesh." J Minim Invasive Gynecol 18, no. 5 (Sep-Oct 2011): 678-81.

III. THE PROSIMA PROCEDURE (AND SIMILAR MESH "KITS") REPRESENTED A SIGNIFICANT DEPARTURE FROM SURGICAL PRACTICES AT THE TIME AND YET ETHICON DID NOT EXERCISE DILIGENCE IN THE DESIGN AND DEVELOPMENT OF THE PROSIMA DEVICE

The Ethicon Prosima device (and other polypropylene mesh "kits" designed for the treatment of pelvic organ prolapse) represented a radical departure from surgical practices at the time of their introduction. Implantation of the Ethicon Prosima, using instruments designed to insert mesh straps with pockets adjacent to the obturator internus muscle or the sacrospinous ligaments, followed by a Vaginal Support Device – Balloon Assembly, was a new procedure and presented special risks and required special surgical skills.[5] These new "systems" were very different from mesh slings used to treat stress urinary incontinence.

The Gynecare Prosima Anterior, Posterior, and Combined Pelvic Floor Repair Systems consist of pre-cut Gynecare Gynemesh PS Mesh implant(s), and instruments to facilitate mesh implant placement and postoperative support. Gynemesh PS is identical to Prolene PS. Ethicon marketed Prolene or use in hernia surgery. The mesh shape is identical in the anterior and posterior devices; however, the instruments differ.[6] The Vaginal Support Device-Balloon Assembly of the system (predicated on a vaginal stent), according to the 510k application, "provides support to the vaginal canal after surgery, thus reducing the possibility of contracture, stenosis, and vaginal canal adhesions. The balloon portion of the assembly is inflated with air, similar to the predicate device, filling the vaginal canal space for the first twenty-four hours. The Vaginal Support Device (VSD) of the assembly is made of silicon, as is the predicate device, and remains in the vaginal canal for up to four weeks, providing continuing support to the vagina and the mesh implants as tissue in-growth occurs.[7] The vaginal stent predicate was designed to maintain the vaginal canal following radiological treatment or surgical procedures to restore, enlarge or create a vagina i.e. maintenance of a "neo-vagina".[8] It is not a device that had been used in prolapse procedures or with synthetic mesh procedures.

When Ethicon first considered introducing Gynemesh (Prolene) for use in anterior prolapse, Ethicon recognized that it was "far from being the ideal material for this indication. However, it was decided that the Gynecare division should launch this product for the following reasons:

- To raise awareness of the possibility of using a mesh for prolapse repair;
- To gain entry into this growing market before competitors;
- To spend time seeking out key surgeons as product champions and

[5] Prior to marketing the Prolift, an Ethicon marketing executive after watching a demonstration observed that the procedure to implant a Prolift would require a "major mind shift" for surgeons. ETH.MESH.02282833; Zyczynski HM, Carey MP, Smith AR, Gauld JM, Robinson D, Sikirica V, *et al.* One-year clinical outcomes after prolapse surgery with nonanchored mesh and vaginal support device. Am J Obstet Gynecol 2010;203:587.e1-8.
[6] Traditional 510(k) Premarket Notification GYNECARE PROSIMA Pelvic Floor Repair System. ETH.MESH.07215395.
[7] Traditional 510(k) Premarket Notification GYNECARE PROSIMA Pelvic Floor Repair System. ETH.MESH.07215395.
[8] Silimed 510k and http://www.silimed.com.br/en/urology/.

- To allow time to carry out further market research into what the ideal product for this indication might be."[9]

At the time the Prosima device was marketed in 2010, there was insufficient scientific evidence that supported utilization of this specific system or Gynemesh, the material used in Prosima.[10] Case reports in the literature described problems with other, similar meshes and Gynemesh specifically. Adverse events were occurring and being reported with all types of vaginal mesh for prolapse repair. There had been complications with some synthetic slings. Surgeons were discussing complications at scientific meetings. "Mesh complications" became a frequent topic at conferences. In fact, the little literature available plus a healthy degree of skepticism should have raised serious questions about the wisdom of the use of mesh kits used for vaginal surgery. In Carey's randomized trial comparing traditional anterior and posterior colporrhaphy with the Prosima precursor, the authors failed to demonstrate any improvement in the treatment of prolapse.[11] Unique mesh complications, including mesh exposure, were reported, resulting in higher reoperation rates in the mesh group. The vagina is known to be a very different environment compared to the abdominal cavity and abdominal wall – areas where mesh had been placed previously.[12] Some of the unique features of the vagina include bacterial contamination,[13] dense innervation and vascularization (controlling sensation and function), close proximity to bowel and bladder, and the need for compliance and distensibility for bowel, bladder, and sexual function.

Although, Ethicon justified the development of mesh kits based on the presumption of high recurrence rates with traditional reconstructive procedures using native tissue repair.[14] However, the underlying assumption of high reoperation rates is not supported by the literature. Using current definitions of "success," traditional surgery has been shown to be effective (with less than 10% reoperation rate) and is not significantly improved by the use of mesh, even in the anterior compartment. According to a recent review by Stanford, most studies show an anatomic success rate around 92% for native tissue repairs – identical to mesh repairs. (Stanford, 2012). When Chmielewski reanalyzed Weber's results from her 2001 study using contemporary,

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[9] ETH.MESH.12009027-35.

[10] ETH.MESH.01160159, Gynemesh Prolene Soft mesh, pre-clinical functionality testing strategy, 11-1-2001, Conclusion: "Based upon the Gynemesh Prolene Soft mesh's product characteristics, intended clinical indications and the use of existing polymer materials, additional pre-clinical functionality testing is not required." *See* Giselle Bonet dep., 102:1-7 ("Q. At the time the Prolift was launched, the Prolift itself had not been studied in clinical studies, correct, meaning the actual packaged product with the preformed mesh and the instruments, that had not been studied clinically, correct? A. Correct.")

[11] Carey, M., P. Higgs, J. Goh, J. Lim, A. Leong, H. Krause, and A. Cornish. "Vaginal Repair with Mesh Versus Colporrhaphy for Prolapse: A Randomised Controlled Trial." BJOG 116, no. 10 (Sep 2009): 1380-6.

[12] ETH.MESH.00164607 ("The vagina is NOT the abdomen (nor similar to any other surgical environment").

[13] P1659; P1627.

[14] ETH.MESH.03904451. Ethicon's rationale for the introducing the Prolift was predicated on the failure rate. However, initial Prolift advertising in 2006 claimed "less than 5% failure rate" at 3 months following implantation. Ethicon internal documents at that time, however, showed an approximately 20% failure rate – "Prof Jacquetin's data has not proved as positive as hoped – showing approx. 80% success rate – The data will be initially presented at IUGA in September. Note that this data is a retrospective study of over 100 patients using TVM technique, not necessarily used with Prolift. This less than 90% success rate forces us to differentiate Prolift from the TVM technique moving forward." ETH.MESH.00741137. Ethicon did not inform doctors that the failure rate at 12 months was 18.4%.

clinically relevant criteria for success, she found only 11% of subjects experiencing anatomic recurrence beyond the hymen, 5% of subjects experiencing symptomatic recurrence, and no subjects requiring surgery for recurrence or complications at 1 year. (Chmielewski, 2011). Most importantly, in this particular circumstance, the inventor of the product performed a randomized surgical trail showing no benefit to use of mesh at 1 year before Prosima was marketed.[15]

Additional studies have confirmed the success of native tissue repairs. Oversand found that 94% of 699 women with native tissue repairs of pelvic organ prolapse expressed subjective satisfaction with low reoperation rates. (Oversand, 2013). Funk et al. examined the records of 27,809 anterior prolapse surgeries from insurance records. Of these, 24.7% included mesh. The 5-year cumulative risk of any repeat surgery was significantly higher for vaginal mesh versus native tissue (15.2 % vs 9.8 %) with a 5-year risk of mesh revision/removal of 5.9%. The 5-year risk of surgery for recurrent prolapse was similar between vaginal mesh and native tissue groups (10.4 % vs 9.3 %). (Funk, 2013). Gutman and Sokol have reported a randomized controlled trial with native tissue vs. mesh-augmented anterior repairs at one and three years. (Gutman and Sokol, 2013). The authors found no objective or subjective benefit, a mesh erosion rate of >15%, and a higher reoperation rate with mesh repairs. All reoperations for recurrence were in the mesh group. The authors concluded that the rate of surgery for recurrent prolapse was no different with or without mesh. The mean time to reoperation for recurrence reported in the literature is twelve years, lending little credence to efficacy results in short term studies. (Hagen, 2006).

No studies show improved anatomical or surgical outcomes using mesh in the posterior or apical compartments. Additionally, reoperation rates are higher in mesh repairs due to the treatment of complications.

Reoperation rates for all repairs with mesh are higher due to the need for surgical management of mesh complications. Current literature suggests that mesh procedures may also promote prolapse in the compartments where mesh is not placed. Withagen et al. studied this issue, finding that "[t]ension-free vaginal mesh treatment of one vaginal compartment prolapse seems to provoke the development of vaginal prolapse in initially unaffected vaginal compartments."[16] In my experience, surgeons are seeing apical (uterus, vaginal vault, or enterocele) prolapse through the scarred distal vagina resulting from mesh repairs. The apical compartment prolapse may be exaggerated after mesh placement because the other vaginal compartments are rigidly fixed in place.

The studies demonstrating good results with traditional prolapse repairs are consistent with my experience and give an accurate representation of success rates following native tissue prolapse repairs. A new surgical innovation, whether involving a device or not, should document equivalent efficacy; equal or superior intraoperative complication rates, post-operative recurrence rates, and re-operation rates before touting their product for widespread use. In

[15] Carey, M., P. Higgs, J. Goh, J. Lim, A. Leong, H. Krause, and A. Cornish. "Vaginal Repair with Mesh Versus Colporrhaphy for Prolapse: A Randomised Controlled Trial." BJOG 116, no. 10 (Sep 2009): 1380-6.
[16] Withagen, M.I. "Does Trocar-Guided Tension-Free Vaginal Mesh (Prolift) Repair Provoke Prolapse of the Unaffected Compartments?". Int Urogynecol J 21 (2010): 271-78.

addition, there should be a description of possible complications, how to avoid them and how to manage them.

IV. THE SERIOUS AND LIFE-CHANGING COMPLICATIONS CAUSED BY THE PROSIMA DEVICE WERE FORESEEABLE AND NOT DISCLOSED TO PHYSICIANS AND PATIENTS

A. The Serious and Life-Changing Complications Caused by the Prosima Device Were Foreseeable

Synthetic mesh implanted in the vagina using a kit such as the Prosima product can cause life-altering and sometimes permanent injury and disability. These complications were foreseeable based on the medical and scientific literature, the known properties of polypropylene, experience with other similar devices, and adverse event reporting. By 2006, there was substantial evidence in the literature describing mesh complications with erosion at a significantly high rate. Ethicon internal documents and studies indicate that postoperative vaginal erosion/extrusion occurred in 14.1% of mesh repairs with Ethicon products. Over 50% of these exposures required surgical treatment.[17] The scientific literature bears this out as well. Female pelvic surgeons, especially those of us in academic positions and referral centers, are spending a great deal of time managing mesh complications and performing challenging and risky mesh explant or removal surgeries. Ethicon knew that Gynemesh PS and its prolapse mesh kitswere associated with a high rate of complications. Ethicon documents supporting this opinion can be found in Section VIII.a.

There is a great deal of scientific literature dealing with the material properties of polypropylene mesh and the host response. Reported mesh characteristics include chronic inflammation and foreign body reaction,[18] bacterial contamination,[19] shrinkage and contraction,[20] fibrosis and scarring,[21] embrittlement,[22] nerve involvement,[23] deformation,[24] and

[17] ETH.MESH.00081035; ETH.MESH.00081083; ETHC.MESH.00080954; ETH.MESH.00081006; ETH-01121-01122; ETH.MESH.00081000; ETH-01322.

[18] Elmer, C., B. Blomgren, C. Falconer, A. Zhang, and D. Altman. "Histological Inflammatory Response to Transvaginal Polypropylene Mesh for Pelvic Reconstructive Surgery." J Urol 181, no. 3 (Mar 2009): 1189-95; Smith, T. M., S. C. Smith, J. O. Delancey, D. E. Fenner, M. O. Schimpf, M. H. Roh, and D. M. Morgan. "Pathologic Evaluation of Explanted Vaginal Mesh: Interdisciplinary Experience from a Referral Center." Female Pelvic Med Reconstr Surg 19, no. 4 (Jul-Aug 2013): 238-41; Iakovlev V., Carey ET, Steege J. "Pathology of Explanted Transvaginal Meshes." International Journal of Medical, Health, Pharmaceutical and Biomedical Engineering 8, no. 9 (2014).

[19] Boulanger, L., M. Boukerrou, C. Rubod, P. Collinet, A. Fruchard, R. J. Courcol, and M. Cosson. "Bacteriological Analysis of Meshes Removed for Complications after Surgical Management of Urinary Incontinence or Pelvic Organ Prolapse." Int Urogynecol J Pelvic Floor Dysfunct 19, no. 6 (Jun 2008): 827-31; Vollebregt, A., Troelstra, A., & van der Vaart, C. H. . "Bacterial Colonisation of Collagen-Coated Polypropylene Vaginal Mesh: Are Additional Intraoperative Sterility Procedures Useful?". International Urogynecology Journal and Pelvic Floor Dysfunction 20, no. 11: 1345-51.

[20] Klinge, U., Klosterhalfen, B., Muller, M., Ottinger, A. P., & Schumpelick, V. "Shrinking of Polypropylene Mesh in Vivo: An Experimental Study in Dogs." The European Journal of Surgery 164, no. 12 (1998): 965-69; Velemir, L., J. Amblard, B. Jacquetin, and B. Fatton. "Urethral Erosion after Suburethral Synthetic Slings: Risk Factors, Diagnosis, and Functional Outcome after Surgical Management." Int Urogynecol J Pelvic Floor Dysfunct 19, no. 7 (Jul 2008): 999-1006; Tunn, R., A. Picot, J. Marschke, and A. Gauruder-Burmester. "Sonomorphological Evaluation

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degradation.[25] Smaller pore, heavier weight meshes, like Gynemesh PS, are thought to intensify these reactions.

Studies also characterize the properties of Gynemesh, specifically. Some examples follow. In a study by Jones, Gynemesh was the stiffest of the meshes studied. Letouzey, et al., measured the shrinkage of Gynemesh with ultrasound over a nine year period in 40 patients. They found a 10% per year shrinkage rate up to 85% at 8 years.[26] Liang (2013) found that Gynemesh caused more vaginal degeneration in primate implantation than other less stiff meshes. Feola (2013) found that Gynemesh resulted in deterioration of the biomechanical properties of the vagina – more so than less stiff meshes.

New studies document the increasing rates of severe complications associated with mesh, the difficulty treating these complications, the need for multiple surgeries, the failure of corrective surgery to alleviate the symptoms in many instances, and the life-changing disabilities women suffer. New onset chronic pain syndromes following mesh implantation are the most difficult conditions to manage. Sadly, many injured women are in worse condition after mesh

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of Polypropylene Mesh Implants after Vaginal Mesh Repair in Women with Cystocele or Rectocele." Ultrasound Obstet Gynecol 29, no. 4 (Apr 2007): 449-52; Feiner, B., and C. Maher. "Vaginal Mesh Contraction: Definition, Clinical Presentation, and Management." Obstet Gynecol 115, no. 2 Pt 1 (Feb 2010): 325-30; Jacquetin, B., and M. Cosson. "Complications of Vaginal Mesh: Our Experience." Int Urogynecol J Pelvic Floor Dysfunct 20, no. 8 (Aug 2009): 893-6.

[21] Klosterhalfen, B., K. Junge, and U. Klinge. "The Lightweight and Large Porous Mesh Concept for Hernia Repair." Expert Rev Med Devices 2, no. 1 (Jan 2005): 103-17; Cobb, W. S., K. W. Kercher, and B. T. Heniford. "The Argument for Lightweight Polypropylene Mesh in Hernia Repair." Surg Innov 12, no. 1 (Mar 2005): 63-9.

[22] Junge, K., U. Klinge, A. Prescher, P. Giboni, M. Niewiera, and V. Schumpelick. "Elasticity of the Anterior Abdominal Wall and Impact for Reparation of Incisional Hernias Using Mesh Implants." Hernia 5, no. 3 (Sep 2001): 113-8; Costello, C. R., S. L. Bachman, B. J. Ramshaw, and S. A. Grant. "Materials Characterization of Explanted Polypropylene Hernia Meshes." J Biomed Mater Res B Appl Biomater 83, no. 1 (Oct 2007): 44-9.

[23] Klosterhalfen, B., K. Junge, and U. Klinge. "The Lightweight and Large Porous Mesh Concept for Hernia Repair." Expert Rev Med Devices 2, no. 1 (Jan 2005): 103-17; Bendavid, R., Lou, W., Koch, A., Iakovlev, V. "Mesh-Related Sin Syndrome. A Surreptitious Irreversible Neuralgia and Its Morphologic Background in the Etiology of Post-Herniorrhaphy Pain." International Journal of Clinical Medicine 5 (2014): 799-810; Iakovlev V., Mekel G., Blaivas J. "Pathological Findings of Transvaginal Polypropylene Slings Explanted for Late Complications: Mesh Is Not Inert [Abstract]." International Continence Society Meeting Annual Meeting (2014); Iakovlev V., Carey ET, Steege J. "Pathology of Explanted Transvaginal Meshes." International Journal of Medical, Health, Pharmaceutical and Biomedical Engineering 8, no. 9 (2014).

[24] Margulies, R. U., C. Lewicky-Gaupp, D. E. Fenner, E. J. McGuire, J. Q. Clemens, and J. O. Delancey. "Complications Requiring Reoperation Following Vaginal Mesh Kit Procedures for Prolapse." Am J Obstet Gynecol 199, no. 6 (Dec 2008): 678 e1-4.

[25] Coda, A., R. Bendavid, F. Botto-Micca, M. Bossotti, and A. Bona. "Structural Alterations of Prosthetic Meshes in Humans." Hernia 7, no. 1 (Mar 2003): 29-34; Costello, C. R., S. L. Bachman, B. J. Ramshaw, and S. A. Grant. "Materials Characterization of Explanted Polypropylene Hernia Meshes." J Biomed Mater Res B Appl Biomater 83, no. 1 (Oct 2007): 44-9.; Iakovlev, V., Guelcher, S., Bendavid, R. "In Vivo Degradation of Surgical Polypropylene Meshes: A Finding Overlooked for Decades." Virchows Arch Suppl 1 (2014): S35; Clave, A., H. Yahi, J. C. Hammou, S. Montanari, P. Gounon, and H. Clave. "Polypropylene as a Reinforcement in Pelvic Surgery Is Not Inert: Comparative Analysis of 100 Explants." Int Urogynecol J 21, no. 3 (Mar 2010): 261-70.

[26] Letouzey V., et al. "Ultrasound evaluation of polypropylene mesh contraction at long term after vaginal surgery for cystocele repair." Int Urogyn J 2009;20(Suppl.2):S205-6.

implantation than they were prior to having the original surgery. These particular severe complications are not seen following traditional surgeries.[27] (Hansen, 2014; Dunn, 2014; Abbott, 2014; Unger, 2014).

During implantation tension is placed on the mesh as the instruments are placed into the pockets of the straps.[28] Not only during implantation but after, the Prosima straps are put under some tension, which may ultimately lead to mesh bunching, wrinkling, and deformation.[29] This issue of deformation of the Ethicon mesh is not explained in the Ethicon literature. Ethicon knew that Gynemesh could cause tissue damage during implantation as well as after implantation due to the inflammatory response of the surrounding tissue to the mesh implant. Support for this opinion can be found in Section VIII.a.

When the mesh deforms and contracts, it becomes a rigid and taut instrument that can saw into the tissue, causing the pain that I see frequently in these patients. This issue was not addressed prior to the introduction of the Prosima device and has turned out to have significant clinical implications. This phenomenon was reported by Feiner and Maher in their paper, Vaginal Mesh Contraction: Definition, Clinical Presentation, and Management, published in 2010. The authors concluded that vaginal mesh contraction is "a serious complication after prolapse repair with armed polypropylene mesh that is associated with substantial morbidity, frequently requiring surgical intervention." (Feiner and Maher, 2010).

Letouzy, et al. reviewed the long-term changes in pelvic mesh volumes over time using three-dimensional translabial ultrasonography and found mean contraction of 30%, 65%, 85% at follow-up durations of 3, 6, and 8 years, respectively. This study demonstrates that the pathological process that causes mesh shrinkage is progressive and there is linear evolution of the contraction rate with time, raising the concerning possibility that mesh contraction continues indefinitely.

From my review of Ethicon documents, I find no evidence that there was a systematic evaluation of the Prosima device, including the shape of the mesh, the instruments that insert in the pockets, and the VSD in the female pelvis, a highly vascularized and innervated area prior to the Prosima System being placed on the market. Ethicon and a small group of surgeons, including Dr. Carey, evaluated the technical aspects of placement of Prosima in cadavers.[30]

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[27] Hansen, B. L., G. E. Dunn, P. Norton, Y. Hsu, and I. Nygaard. "Long-Term Follow-up of Treatment for Synthetic Mesh Complications." Female Pelvic Med Reconstr Surg 20, no. 3 (May-Jun 2014): 126-30; Dunn, G. E., B. L. Hansen, M. J. Egger, I. Nygaard, A. C. Sanchez-Birkhead, Y. Hsu, and L. Clark. "Changed Women: The Long-Term Impact of Vaginal Mesh Complications." Female Pelvic Med Reconstr Surg 20, no. 3 (May-Jun 2014): 131-6; Abbott, S., C. A. Unger, J. M. Evans, K. Jallad, K. Mishra, M. M. Karram, C. B. Iglesia, C. R. Rardin, and M. D. Barber. "Evaluation and Management of Complications from Synthetic Mesh after Pelvic Reconstructive Surgery: A Multicenter Study." Am J Obstet Gynecol 210, no. 2 (Feb 2014): 163 e1-8; Unger, C. A., S. Abbott, J. M. Evans, K. Jallad, K. Mishra, M. M. Karram, C. B. Iglesia, C. R. Rardin, and M. D. Barber. "Outcomes Following Treatment for Pelvic Floor Mesh Complications." Int Urogynecol J 25, no. 6 (Jun 2014): 745-9.

[28] ETH.MESH.12608542-51; ETH.MESH.02341398.

[29] ETH.MESH.02589066-02589068; Kirkemo dep. (4-18), at p.135-138, p.150; Hinoul dep. (4-6), p.506-507.

[30] E.g., ETH.MESH.02999594; Reisenauer, C., T. Shiozawa, M. Huebner, M. Slack, and M. P. Carey. "Anatomic Study of Prolapse Surgery with Nonanchored Mesh and a Vaginal Support Device." Am J Obstet Gynecol 203, no. 6 (Dec 2010): 590 e1-7.

However, cadavers are not a substitute for *in vitro*, *in vivo* studies of the mesh or careful Investigation using laboratory animals or human trials. It is well known that cadaveric tissue does not maintain the same properties that are present in the tissue of a living human being. The main benefit of the cadaver model is to demonstrate gross anatomical landmarks, but a hemi-pelvis from a cadaver does not help the surgeon to understand individual anatomical variations. A cadaver cannot be used to evaluate the tissue response, nerve or blood vessel damage, anatomic or functional outcomes, safety concerns, or in vivo characteristics of the product. Support for these opinions can be found in Section VIII.a.

The serious complications associated with transvaginally placed mesh kits are now well-known to surgeons practicing in the area of female pelvic reconstructive surgery, and well-described in the medical literature. If Ethicon had performed the indicated testing before clinical marketing proceeded, including bench testing, animal studies, clinical trials, and examination of explanted meshes, these problems would have been identified.

B. Ethicon knew about complications associated with their products and did not inform doctors as to how to manage them

I have reviewed the Ethicon Instructions for Use (IFU) and patient and doctor brochures for these products. Reviewing the information contained in these documents is something I do on a regular basis in my practice and in my capacity as an educator of medical students, residents, and colleague physicians. In my opinion, these documents do not provide adequate information for doctors and patients to make informed choices. They do not include the severity and frequency of the complications, a complete list of potential complications, the lack of clinical data to support their use, the difficulty in removing mesh, and the occurrence of permanent disability. The product literature also does not provide information regarding contraindications to the use of the product in women with fibromyalgia, painful bladder syndrome, or other chronic pain conditions. Dr. Carey, in his prospective randomized trial, listed several contraindications to transvaginally placed mesh including prior pelvic radiation therapy and immunocompromised; neither is listed in the Prosima IFU.[31] Ethicon documents supporting this opinion can be found in Section VIII.b.

The most obvious complication missing from the adverse reaction list is chronic pain. Severe and intractable pain following mesh prolapse repair is the most serious problem I see regularly in patients referred to me for the treatment of mesh complications. Ethicon knew that chronic pain could be a significant postoperative problem when these products are utilized in vaginal surgery, and yet it is not mentioned in Prosima 510(k) application, labeling (IFU), or physician and patient education materials. Even though postoperative pain can occur with traditional prolapse surgery (vaginal prolapse repair with native tissue utilizing sutures or abdominal sacrocolpopexy), debilitating, life-altering pain following these procedures has rarely been a significant issue. When post-operative pain occurs, it is usually temporary, treatable, and typically does not result in long-term disability. Pain as a result of mesh kits, using Gynemesh is often life-altering and can be permanent. Ethicon was aware of this lack of viable treatment

[31] Carey, M., P. Higgs, J. Goh, J. Lim, A. Leong, H. Krause, and A. Cornish. "Vaginal Repair with Mesh Versus Colporrhaphy for Prolapse: A Randomised Controlled Trial." BJOG 116, no. 10 (Sep 2009): 1380-6.

options for mesh-related chronic pain conditions. Ethicon should have investigated whether pain complications could be avoided. If they do occur, Ethicon should have developed protocols and treatment recommendations prior to marketing a permanently implanted medical device.

Another serious problem involves the removal of transvaginally placed mesh when complications do arise. Corrective surgeries for mesh complications are often lengthy, risky (due to the potential for further damage to nerves, bladder and bowel, and further scarring and retraction), invasive, and frequently do not completely resolve the problem. When urogynecolgists started seeing these severe complications, there were no established treatment guidelines. Many specialists now have a significant portion of their practices occupied with handling mesh complications. Ethicon should have considered how to avoid or if unable to avoid how to manage the complications that they knew would occur and developed protocols for their management. Ethicon should also have communicated these protocols to the physicians they were training to implant their Prosima device.

The Prosima IFUs stated throughout the time the product was on the market that: "The mesh remains soft and pliable, and normal wound healing is not noticeably impaired. The material is not absorbed, *nor it is subject to degradation* or weakening by the action of the tissue enzymes."[32] There was absolutely nothing in the literature to support that claim. Ethicon failed to inform physicians and patients accurately and completely through the labeling and marketing materials. This information would have been important to physicians in evaluating the risks and benefits of the Prosima device which was intended to be a permanent implant for the life of the patient. This information would also have been important for physicians to know in order that they might have a complete informed consent discussion with their patients.

In its marketing materials, Ethicon described Prosima as a "unique product addressing a different grade of prolapse and target audience utilizing a novel technique" and as the "first fixationless mesh kit with anatomical and functional proof in symptomatic moderate prolapse." However, there is no definition of moderate prolapse and in the IFU there is no absolute contraindication to its use in any degree of prolapse.[33] However, feedback from physicians raised concerns about complications, as well as the effectiveness of this new procedure. Ethicon should have considered how to avoid, recognize, and manage the complications that they knew would occur and developed protocols for their management. Ethicon should also have addressed these complications and communicated the protocols to the physicians they were training to implant their Prosima devices.[34]

Other well-known complications Ethicon failed to cite in their warnings include nerve damage (sometimes permanent), vaginal scarring,[35] de novo stress urinary incontinence, other bladder and bowel dysfunction, impairment of sexual function, foreign body reaction to synthetic

[32] ETH.MESH .02341526 (emphasis added). The IFU maintained this claim throughout the time the Prolift was on the market.
[33] *Id*.
[34] ETH.MESH.10608341; ETH.MESH.06773944; ETH.MESH.06900544; ETH.MESH.05009194; ETH.MESH.04098598; ETH.MESH.03162936.
[35] ETH.MESH.03021946 ("Pelvic Floor materials are still over-engineered . . . we need less foreign body material . . we need: Materials that correlate to measured female pelvic physiological characteristics."

products, chronic infection, recurrence of prolapse, and partner discomfort or injury with sexual intercourse. But the most intriguing item in the IFU is listed under warnings and precautions: "Do not use the GYNECARE PROSIMA System if you think the surgical site may be infected or contaminated." This warning requires that no surgeon use the Gynecare Prosima device transvaginally because all vaginal surgical fields are contaminated. Therefore, it can be confidently stated that Gynemesh has no place in vaginal surgery.

At the time the Prosima was marketed and sold, Ethicon was aware of issues with erosion, infection, scarification, and the significant problems these issues could create.[36] However, I could not find any Ethicon documents advising surgeons how to treat these complications. The warning label should have stated that polypropylene lasts a lifetime and complications may require additional surgeries that may or may not correct the newly acquired problems. Doctors should have been told that these complications were serious and could be life-altering for their patients.

The Prosima IFU trivializes the risks with this particular device by stating that the "potential adverse reactions are *those typically associated with surgically implantable materials*" and that "potential adverse reactions are those *typically associated with pelvic organ prolapse repair procedures*, including pain with intercourse and pelvic pain. These may be self-resolving overtime." In fact, there has been reported multiple times that new onset pelvic pain may never be resolved despite aggressive treatment. It was well known that many complications are unique to transvaginally placed mesh devices and can be life-changing and permanent.

C. Ethicon did not inform doctors as to which patients were poor candidates for the Prosima procedure

The IFUs for the Prosima product include the following contraindication: "When GYNECARE GYNEMESH PS mesh is used in infants, children, pregnant women, or women planning future pregnancies, the surgeon should be aware that this product will not stretch significantly as the patient grows."[37] There is nothing to document specifically who would most likely benefit from the product use. Patient selection is important. Ethicon should have determined and informed doctors what subpopulations of women were appropriate candidates for their products or more importantly who is not a satisfactory candidate.

When a device, operation, or implantable material does not have a proven track record, this information can only be obtained through clinical trials or unfortunately adverse event reporting such as the 2008 and 2011 FDA warnings which detailed injuries experienced by

[36] P.1659.

[37] ETH.MESH.02341522; ETH.MESH.02341454. In 2009, Ethicon added contraindications: "GYNECARE GYNEMESH"' PS Mesh must always be separated from the abdominal cavity by peritoneum. GYNECARE GYNEMESH"' PS Mesh must not be used following planned intra-operative or accidental opening of the gastrointestinal tract. Use in these cases may result in contamination of the mesh, which may lead to infection that may require removal of the mesh. The GYNECARE PROLIFT' System should not be used In the presence of active or latent infections or cancers of the vagina, cervix, or uterus." ETH.MESH.02341734.

women from vaginal surgical mesh.[38]. One example is the use of these prolapse mesh kits in women who have a pre-existing history of chronic pelvic pain. It is my opinion that mesh products should not be used in women with a history of chronic pelvic pain. Ethicon documents confirm that its mesh products, including Prosima, are contraindicated in patients with chronic pain conditions.[39]

Another example where extreme caution should have been used is in women who are sexually active. It is my opinion that the risk of dyspareunia is unacceptably high following the placement of a prolapse mesh kits and that they should not be used in women who are sexually active unless the patient is extensively counseled on the possibility that her sexual function will be significantly and permanently impaired.

Studies after commercialization of the Prosima/Prolift suggest that patients who have diabetes and women who smoke have a much great risk of erosion. Ethicon should have alerted surgeons to this information so that they could properly counsel their patients.

V. THERE ARE SAFER ALTERNATIVES TO THE USE OF THE PROSIMA MESH KIT THAT ARE EFFECTIVE AND HAVE VIRTUALLY NONE OF THE DEVASTATING COMPLICATIONS SEEN WITH THIS PRODUCT

There are safer alternatives to the Prosima mesh device. As discussed previously, the whole premise of transvaginal mesh kits was based on the inaccurate perception of high recurrence rates when traditional reconstructive procedures using native tissue repair were performed. The success of native tissue repairs is even more apparent when mild to moderate prolapse repairs are considered – the indication for Prosima. However, the underlying assumption of high rates of recurrence and reoperation for prolapse is not supported by the literature. Devastating complications associated with Gynemesh could have been predicted and did, in fact, occur. These severe complications had virtually never been reported with traditional native tissue repairs. Unlike mesh repairs including the Prosima procedure, short and long term complications of native tissue repairs are known and the treatments are well-established.

For surgical treatment of cystocele, an anterior colporrhaphy or site-specific native tissue repair using suture is quite effective with clinical success rates of about 90%. Complications are infrequent, treatable, and related to the surgery itself and the immediate post-operative period. Of course, mesh erosion does not occur. Other complications, such as chronic pain or debilitating dyspareunia are uncommon. Dr. Carey's original randomized trial comparing native tissue to Gynemesh repairs did not find a benefit to the use of mesh. In subsequent studies investigating the Prosima device, a native tissue arm with addition of the VSD only (and not the Gynemesh) might have demonstrated benefits from the use of the VSD without incurring the problems associated with Gynemesh PS.

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[38] Administration, Food and Drug. "Surgical Mesh for Treatment of Women with Pelvic Organ Prolapse and Stress Urinary Incontinence." edited by Obstetrics & Gynecology Devices Advisory Committee. http://www.fda.gov/downloads/UCM270402.pdf, 2011.

[39] ETH.MESH.00070065.

A rectocele is traditionally treated with posterior colporrhaphy, a procedure to plicate the subepithelial vaginal connective tissue. Painful intercourse can occur following a posterior repair, but is uncommon as a long-term problem.

Surgical options for women with vaginal apical prolapse include transvaginal suspension procedures using native tissue and sutures, such as sacrospinous ligament fixation and uteroscaral ligament suspension or sacral colpopexy, which can be performed abdominally, laparoscopically, or robotically. Although sacral colpopexy uses synthetic mesh, it does not have the same risks of new onset pelvic pain or adverse effects on vaginal volume and sexual function as does mesh placed transvagainally.

In 2000, I published our experience at Scott and White with apical prolapse treated with transvaginal reconstructive surgery with native tissue. In this series of 302 patients, 87% had optimal anatomic outcomes, with no persistent or recurrent support defects at any site. Thirteen percent had one or more sites with some degree of loss of support, but the majority of these were grade I defects detectable only on careful pelvic exam. Morbidity included a 1% transfusion rate, a 1% ureteral injury or ureteral kinking rate, and a 0.3% postoperative death rate (an 85 year old woman with dementia died at home 4 days after the surgery with no autopsy). None of the ureteral injuries resulted in permanent disability. (15). We also reported on the recognition and management of nerve entrapment pain after uterosacral ligament suspension. Eight (1.6%) of 515 patients had neuropathic pain postoperatively that was treated immediately by removing the sutures on the affected side. In all patients, the pain resolved. (16). This situation is very different from the nerve injuries and complex neuropathic pain conditions that I see with mesh. With mesh-related neuromuscular pain, the location is variable, the pain can present immediately or remotely, and the new onset pain can be very difficult to treat, often requiring more than one operation and with less than optimal success.

Paraiso et al. (1996) reported on 243 patients (mean follow-up 73.6 months) who underwent sacrospinous ligament suspension and pelvic reconstruction. Recurrence of prolapse occurred over time, but only 4.5% underwent subsequent pelvic reconstructive surgery. Defect-free survival rates at 1, 5, and 10 years were 88.3%, 79,7, and 51.9%, respectively. I had the opportunity to review this manuscript and write the Comment. I noted the importance of the following principles needed for successful reconstructive surgery: 1) correction of all anatomic defects; 2) maintenance or restoration of normal bowel and bladder function; and 3) maintenance of the vaginal canal for sexual function. Attempting to use a standardized operation with mesh kits when an individualized approach is required invites problems after surgery. Operations for prolapse require diagnostic acumen and technical execution of a procedure that is tailored to the individual patient's anatomy, symptoms, and desires.

Dr. Marcus Carey, the inventor of the Prosima device, conducted a prospective, randomized, ethics committee approved study beginning February 2003 of which the primary objective was to compare vaginal repair augmented by mesh with traditional colporrhaphy for the treatment of pelvic organ prolapse. He completed the recruitment of 139 women in August 2005. The women were treated surgically by either standard colporrhaphy using absorbable sutures or by the placement of Gynemesh PS which has been soaked in antibiotic solution. These women were reevaluated 12 months following index surgery with main outcome measure

being absence of POP-Q ≥ 2 prolapse at 12 months. In the conclusion drawn from data analysis, Dr. Carey found that vaginal surgery augmented with mesh did not result in significantly less recurrent prolapse than traditional colporrhaphy at 12 months following surgery. In addition, 5.6% of women in the mesh group experienced mesh exposure.[40] Despite the fact that the study completed all recruitment and enrollment in 2005 and the 12 month follow up would have ended in August 2006, the data was not published until 2009, almost 3 years after data collection ended. However, this information was available to the inventor and Ethicon before Prosima was marketed as noted in Ethicon internal documents dated December 2006.

A subsequent article by Carey and Slack reported on the use of Gynemesh and a vaginal support device. The patient population was recruited June 2004 and February 2005. The study objective was to describe a new surgical procedure for pelvic organ prolapse and report results of surgery. Interestingly enough, this article was accepted for publication in October 2007, two years before Dr. Carey's manuscript on the results of his original group of randomized patients was reported. The new surgical procedure article in which Dr. Carey and Dr. Slack describe the basic concepts of Prosima, there was no comparison to any other procedure or technique not using mesh or vaginal support device. If the authors had used the intention to treat method or analysis, the failure rate would have been as high as 28.4 %. Instead they chose to report only on the patients that returned for follow up. Using this best case scenario, there was still a 15% recurrence rate. In their experienced hands there was one rectal injury and four mesh exposures.

Another article, "One-year clinical outcomes after prolapse surgery with nonanchored mesh and vaginal support device" was co-authored by a group called the Prosima Study Investigators. The Prosima Study Investigators were in fact composed of experienced gynecologic surgeons from three continents, the inventor of device, and employees of Ethicon. The surgical investigators were required to undergo "[c]entral training comprised review of the manufacturer's instructions for use, cadaveric dissection with device placements, and observation of live surgery . . . Investigators who were unfamiliar with the device performed at least 1 anterior and posterior procedure under the observation of a development team member" before collecting surgical data. Despite these surgeons' credentials, experience, and preparation, their results included two cystotomies and mesh exposure in 8% of the patients by the 12-month postoperative evaluation. 21.93% of patients had ≥ stage 2 prolapse at the end of the one year follow up.

A timeline of when these studies were initiated, follow up ended, and when data became available:

- August 1998: Ethicon states "PROLENE is far from being the ideal material".
- February 2003-August 2005: Dr. Carey enrolls patients in RCT comparing native tissue to Gynemesh vaginal repairs.

[40] Carey M, Slack M, Higgs P, Wynn-Williams M, Cornish A. Vaginal surgery for pelvic organ prolapse using mesh and a vaginal support device. BJOG 2008;115:391–397.

- 2004: Ethicon reaches contract agreement with Dr. Carey regarding Prosima.[41]

- June 2004-Februry 2005: Drs. Carey and Slack enrolled patients for a prospective, observational study of Gynemesh repairs with VSD.

- December 2006: Data from Dr. Carey's RCT comparing native tissue to Gynemesh. Data showed no benefit in the Gynemesh group and increased complications of mesh exposure and was available to Ethicon.

- February 2007: Prosima cleared for marketing in the United States.

- October 2007: Drs. Carey's and Slack's Gynemesh+VSD study was accepted for publication. However, early analysis of the data was available to Ethicon in Dec 2006 meeting.

- 2007: Patients recruited by Prosima Investigation Group (Dr. Carey, Ethicon employees and others).

- July 2009: Carey RCT published. Data showed no benefit in the mesh group and increased complications.

- December 2010: Zyncynski, Carey, and Ethicon employees publish one-year data from Prosima Study Group, but it had already been presented in April and June 2009 at National and international meetings.

When Ethicon marketed the Prosima, the IFU stated that "[t]raining on the use of the GYNECARE PROSIMA Pelvic Floor Repair Systems is recommended and available. Contact your company sales representative to arrange for this training." Unlike these highly skilled surgeons in the Prosima Study Investigators group, who were required to have read the IFU's, do cadaver dissection with device in place, and observe live surgical use of the Prosima system, the surgeons to whom Prosima was marketed could or could not request training. In the case that they request training, training is not specifically defined in the IFU. There are no data to support the presumption that Prosima users could produce clinical results equal to those obtained by the experienced Prosima Study Investigators who underwent rigorous pre-implantation training.

I reviewed the full-length articles published on the Prosima device. I also reviewed Ethicon documents raising serious questions about the quality and validity of Prosima studies.[42] I performed a PubMed search for full length articles regarding the Prosima devices. The first article published was by Carey in 2008,[43] the inventor of the Prosima who later would receive royalties from Ethicon. He used a hand cut piece of Gynemesh which differed between the anterior and posterior compartments, his own selected instruments, and a VSD in three sizes –

[41] ETH.MESH.09268043
[42] ETH.MESH.03912703; ETH.MESH.03162936.
[43] Carey M, Slack M, Higgs P, Wynn [illegible] "Vaginal surgery for pelvic organ prolapse using mesh and a vaginal support device." BJOG 2008;115:391-7.

not the Prosima. He reported outcomes at 6 and 12 months; however, 16% of patients did not complete the I year exam. In his series, considering the best case scenario, 15% of patients developed objective prolapse, with 58% of these occurring in the compartment that did not receive a mesh repair. The authors concluded: "Further clinical studies, including comparative studies are required to establish the role of this surgery." Comparative studies were never performed.

Reisenauer (and other Prosima Study Investigators, including Carey) performed a cadaver study in 2010[44] and "confirmed the accurate and safe placement of the polypropylene implants with the use of the prescribed surgical technique." As mentioned elsewhere in this report, a cadaver study does not provide reliable data regarding safety and efficacy. Zyczynski[45] and Sayer[46] reported on the 1 and 2 year outcomes of the Prosima study. Carey was an author on the first paper. Ethicon employees were also authors. Only 80% of patients completed the 2-year follow-up. The exposure rate in this series was found to be 9.1%. Success, as defined as leading edge above hymen, was 78.3% at I year and 76.4% at 2 years. When using POP-Q assessment, the results were 77.1% at 1 year and only 69.1% at 2 years.

A study by Tsai (2014)[47], with short-term follow-up (3-6 months), reported an 8% exposure rate and 16% anatomic recurrence. Only one-third of sexually active patients had resumed intercourse. De novo SUI occurred in 5.4% and de novo urge incontinence in 4.7% - even with 30% receiving concomitant mid-urethral slings. Zhang (2015)[48] reported a series of Chinese women receiving Prosima at 12 months follow-up. The authors found that 25% of patients experienced voiding difficulty and 35.4% had vaginal mesh contraction or exposure. The anterior compartment was particularly prone to recurrence and vaginal complications. The authors concluded that the procedure carried a "low postoperative patient satisfaction rate and a high risk of mesh complication."

After reviewing the Prosima literature, it is my opinion that these articles do not support the safety and efficacy of the device. The results raise serious concerns. Additionally, there are no comparative studies, numbers are small, there is no long-term follow-up, and there are flaws in the methodology.

VI. ETHICON DID NOT PERFORM PROPER CLINICAL TRIALS TO DEMONSTRATE THE SAFETY AND EFFICACY OF ITS DEVICES

[44] Reisenauer C, Shiozawa T, Huebner M, Slack M, Carey MP. Anatomic study of prolapse surgery with nonanchored mesh and a vaginal support device. Am J Obstet Gynecol 2010;203:590.e1-7.
[45] Zyczynski HM, Carey MP, Smith AR, Gauld JM, Robinson D, Sikirica V, *et al.* One-year clinical outcomes after prolapse surgery with nonanchored mesh and vaginal support device. Am J Obstet Gynecol 2010;203:587.e1-8.
[46] Sayer T, Lim J, Gauld JM, Hinoul P, Jones P, Franco N, *et al.* Medium-term clinical outcomes following surgical repair for vaginal prolapse with tension-free mesh and vaginal support device. Int Urogynecol J 2012;23:487-93.
[47] Tsai et al., Factors that affect early recurrence after prolapse repair by a nonanchored vaginal mesh procedure, Taiwanese Journal of Obstetrics & Gynecology 53 (2014) 337e342
[48] Zhang et al., Tension-free Polypropylene Mesh-related Surgical Repair for Pelvic Organ Prolapse has a Good Anatomic Success Rate but a High Risk of Complications, Chinese Medical Journal; February 5, 2015, Volume 128:Issue 3.

From my review of the materials referenced, I was impressed by the clear absence of any systematic approach on the part of Ethicon with regard to the clinical testing of their products, including Gynemesh, prior to placing the products on the market. Scott Jones, Product Director for Ethicon, acknowledged that one option available to Ethicon regarding the marketing of another Ethicon kit using Gyenmesh was to not make the Prolift commercially available until clinical trials could be conducted to establish that the Prolift, including transvaginally placed Gynemesh, product and procedure was safe and effective, but Ethicon chose to go directly to market:

> Q. Certainly one of the options to Ethicon would have been to not sell the Prolift® on a widespread commercial basis as it was and instead just limit it to experimental clinical trials until there could be solid confidence throughout the medical community that this was a safe and effective procedure and product. That was an option that Ethicon had. Correct?
>
> A. I suppose it's always an option with any product or any company.
>
> …
>
> Q. Ethicon had the option to not make the Prolift® commercially available unless and until carefully controlled long-term clinical trials could prove it to be safe and effective enough to justify whatever risks there were, but rather, Ethicon chose not to do that, instead just sell it commercially as it did. Correct?
>
> A. Ethicon did choose to commercially sell the product, if that's what the question is.[49]

Although these statements were made in regards to Prolift, a kit which also uses Gynemesh placed tranvaginally, the same options applied to Prosima. Ethicon documents state that "little to no testing" of the mesh and inserters would be done to support the safety of the Prosima device and that "no direct animal model" would be done to support the efficacy of the Prosima device. Prosima was not adequately studied before it was launched. [50] Early data on Prosima would not support its safety and efficacy. As discussed earlier in this report, Ethicon knew as early as 2006 that there were concerns regarding preliminary data, and Ethicon internal documents demonstrate that Ethicon Employees were aware of the outcomes of Carey's randomized clinical trial and that the study "would not support Prosima directly."[51] Despite this, the full text manuscript presenting Carey's data was not published until 2009, almost three years later. Ethicon had knowledge of Carey and Slack's observational study, and specifically commented on the loss to follow up in December 2006.[52] Ethicon was aware of loss to follow up and the concerning results; however, the data were not published for another 2 years. That leads to a reasonable conclusion that this data was available to Ethicon

[49] Jones dep., 727:19-728:4; 728:25-729:10.
[50] ETH.MESH.02999594; ETH.MESH.03049945; ETH.MESH.000955676; ETH.MESH.04569706; ETH.MESH.06148459; ETH.MESH.03960706; ETH.MESH.06312970; ETH.MESH.11915987; ETH.MESH.03049713;
[51] ETH.MESH.03912703.
[52] *Id*.

in 2006, 2-3 years before either manuscript was published. However, Ethicon continued with the development and marketing of Prosima, when in fact its own documents cite to the "disappointing results" of the Carey/Slack study which Ethicon states "was considered as very important" to support the Prosima.[53]

A critical analysis of these devices and how they would function inside a woman's body was never made before the devices were placed on the market. There were no proper randomized controlled trials with institutional review board (IRB) approval performed in the United States or abroad prior to selling these products.[54] Ethicon was aware of the lack of clinical data and the implications of not having this data. Support for this opinion is contained in Section VIII.c.

At the same time, Ethicon ignored significant evidence in the literature and their own experience with hernia mesh and Gynemesh PS mesh that would have led any reasonable person to expect the product to cause significant complications and risks.

Overlaying these inadequacies was the complete lack of any long-term studies establishing the safety and effectiveness of the Prosima Systems. Such studies establishing the long-term safety and efficacy of the Prosima Systems were never conducted. Importantly, there were no studies with sig longitudinal follow up comparing the safety and effectiveness of the Prosima Systems with traditional vaginal prolapse surgery.

If the Prosima device was to be used at all, it should only have been used in the context of a rigorous scientific clinical trial. Such trials require strict guidelines, with a limited and carefully selected patient population, and only with an extensive informed consent process designed to clearly notify participants that the use of the Prosima System was purely experimental, that the safety and effectiveness could not be reliably stated (hence, the need for clinical study), and that significant, life-altering complications could result, which could be untreatable.

Ethicon failed to establish a data registry for the Prosima that would have enabled it to track the results in real clinical practice. Surgeons using the device and providing feedback confirmed that data registries are more "reflective of real world experience," because: "Clinical studies use Tier 1 docs [doctors], real world experience is heavily weighted with the outcomes produced by Tier 2 and 3 doctors. Data registries more reflect the real world in the eye of many of those docs."[55] A registry would have been a very useful tool to track the outcomes of patients who underwent the Prosima procedure, a permanently implanted Gynemesh product.

As a physician and surgeon, I expect companies to provide me with complete and

[53] ETH.MESH.03162936, ETH.MESH.03910723
[54] ETH.MESH.01160159, Gynemesh Prolene Soft mesh, pre-clinical functionality testing strategy, 11-1-2001, Conclusion: "Based upon the Gynemesh Prolene Soft mesh's product characteristics, intended clinical indications and the use of existing polymer materials, additional pre-clinical functionality testing is not required."
[55] ETH-49659.

accurate information regarding the safety and efficacy of their products. This information cannot be provided without sufficient scientific and clinical data.

In order to evaluate these products in any meaningful way, the entire device and procedure should have been used in testing. Issues such as graft tension, maintenance of graft orientation, shrinkage tendencies, deformation of the mesh (folding, bending, bunching, and cording), potential nerve and blood vessel injuries, histologic indicators of immune and inflammatory reactions, and impact on sexual function, bladder, and bowel function should have been studied prior to commercial introduction. Outcomes, complications, and the best ways of avoiding and/or managing complications should have been resolved prior to marketing.

Documents supportive of this opinion can be found in Section VIII.c.

VII. THE MEDICAL LITERATURE DOES NOT SUPPORT THE USE OF MESH KITS FOR THE SURGICAL TREATMENT OF PELVIC ORGAN PROLAPSE.

Gynemesh PS and Prosima, implanted in the vagina, can cause life-altering and sometimes permanent injury and disability - without proven benefit. The literature now bears this out. Urogynecologists, especially those of us in academic positions and referral centers, spend a great deal of our time managing mesh complications and performing challenging and risky mesh removal surgeries.

I have reviewed the reliable scientific literature regarding the use of transvaginal mesh for prolapse repair. From these studies (and confirmed by my clinical experience), I have made the following conclusions regarding the efficacy of these products:

1. There is no good evidence supporting improved benefit in quality of life (QOL) or relief of symptoms *in any compartment* with the use of transvaginal mesh for the treatment of pelvic organ prolapse.
2. There is no reduction in reoperation rates for prolapse *in any compartment* with the use of transvaginal mesh for the treatment of pelvic organ prolapse.
3. There is no evidence of anatomic benefit with the use of transvaginal mesh for the treatment of pelvic organ prolapse in the posterior or apical compartments.
4. Initially it appeared as if there might be some *anatomic* benefit in the anterior compartment. These findings are now reliably disputed and any anatomic benefit obtained is frequently a result of scarring and at the expense of proper function.
5. The total number of reoperations is higher in mesh repairs due to the rate of surgeries for repair of complications.

I have made the following conclusions regarding the safety of these products from my review of the scientific literature:

1. Adverse events and complications are common.
2. Many of these complications do not occur with traditional prolapse repairs.
3. Many of these complications are life-altering and permanent, unlike those seen with traditional prolapse repairs.

4. Many of these complications require additional surgery which may *or may not* alleviate the symptoms - unlike traditional prolapse repairs.
5. Sometimes, multiple surgeries are required.
6. These complications can occur at any time – months or years after the original surgery, unlike complications occurring with traditional prolapse repairs.
7. Explant surgery, when indicated, is risky, difficult to perform, and may or may not alleviate symptoms.

I have concluded the following regarding the differences between mesh complications and those associated with traditional surgery:

1. Many of the complications reported occur only with mesh. These include erosion and extrusion, mesh contraction syndrome, affecting vaginal volume and distensibility, organ perforation from mesh, partner injury, severe vaginal pain, granulomas, and need for multiple surgical procedures for removal and attempted relief of pain.
2. Mesh complications, as opposed to complications with traditional repairs, are likely to be more frequent and more severe. Examples include dyspareunia, de novo stress urinary incontinence, chronic pelvic pain, neuromuscular injury, and emotional sequelae.
3. Most mesh complications are more difficult to treat. This includes fistulae, bleeding, infection, bowel/bladder injuries, dyspareunia, pelvic pain, and recurrent prolapse.
4. The potential for complications lasts indefinitely because the synthetic mesh is permanent and virtually impossible to remove in its entirety.
5. Some risks are still unknown and cannot be known for many years to come.

These opinions are based on a broad familiarity with the medical literature. The FDA reached many of these same conclusions in its white paper on the use of transvaginal mesh dated July 2011. Additional publications have appeared in the literature since the time of its publication, offering further support for these opinions. (e.g. Abbott, 2014; Lee, 2014). In short, the risks of mesh kits for transvaginal prolapse repair (such as Prosima) far outweigh any benefits.

VIII. EXAMPLES OF ETHICON DOCUMENTS SUPPORTING THESE OPINIONS

The following sections give examples of Ethicon documents I have reviewed which support my opinions, but the supportive documents are not limited to those that are shown below.

a. Complications Caused by the Prolift Devices Were Foreseeable

ETH.MESH.01220730: (2/10/2004)

- Erosion is still a primary concern because it is the symptom or result of the scar formation around and on the mesh. The identification of the collagen fibrils' orientation and eventual contraction will be the measurement of how well we are succeeding in reducing the scar formation. The two are both important and I would use one to identify the potential for the other in this early stage work.

- What are the other materials/construct ideas being considered by Gynecare as second generation products to Gynemesh PS?

Redacted

- Additionally, I am open to other alternate material suggestions.

Contraction of Scar Tissue

- Has contraction of scar tissue been reported with use of Gynemesh PS?
- Yes it has. However, the only way it is specifically identified is when the repair fails and the surgeon needs to re-operate. Otherwise the complications which could indicate scar contraction, such as pain or tension (i.e.pulling or pressure) in normal circumstances can not be directly identified as due to the contraction, because every thing is internal and can not be seen. Also, female sexual dysfunction due to pain can be attributed to an over tightening of the vaginal tissue or scar adhesions between the vagina and rectum or bladder.

ETH.MESH.00584846

From: Kammerer, Gene [ETHUS]
Sent: Mon, 10 May 2004 16:20:27 GMT
To: Melican, Mora [ETHUS] <MMELICAN@ETHUS.JNJ.COM>; Brown, Kelly [ETHUS] <KBrown8@ETHUS.JNJ.com>; Gosiewska, Anna [ETHUS] <AGosiews@ETHUS.JNJ.com>
CC: Walji, Zenobia [ETHUS] <ZWalji2@ETHUS.JNJ.com>
Subject: FW: Mesh for TVM

Here is some input from the Gynecare European unit regarding mesh used for pelvic floor repair. Pro. Jacquetin is the inventor of the Pelvic floor repair technique Gynecare will be marketing next year. We are working very closely with him and Dr. Cosson to develop it. Based on this information and other communications I have had it seems our competition is ahead of us in this area. We need to think about how we can fast forward this project, get more support from both Gynecare and Ethicon as well as quickly optimize the construction. Kelly, let's add this in to our meeting agenda tomorrow.

Gene
-----Original Message-----
From: Berthier, Ophelie [JNJFR]
Sent: Monday, May 10, 2004 11:39 AM
To: Walji, Zenobia [ETHUS]
Cc: Bonet, Giselle [ETHUS]; Kammerer, Gene [ETHUS]; Arnaud, Axel [JNJFR]
Subject: Mesh for TVM

Zenobia,

I know you are working on new mesh materials with Gene and I'd like to share with you the inputs of Pr Jacquetin and Dr Cosson.

Their main concern is now the shrinkage of the mesh which may lead to pain, dyspareunia...Indeed now that they have tremendously improved the technique and lowered the erosion rate what needs to be improved is the shrinkage of the mesh (in this case gynemesh soft).

ETH.MESH.00681364

From: Walji, Zenobia [ETHUS]
Sent: Tue, 07 Sep 2004 13:50:29 GMT
To: Bonet, Giselle [ETHUS] <GBonet3@its.jnj.com>; Bell, Steve [ETHIT] <SBell6@ethit.JNJ.com>
CC: Mahar, Kevin [ETHUS] <KMahar@its.jnj.com>; Breznak, Mike [ETHUS] <MBREZNAK@ETHUS.JNJ.com>
Subject: FW: Pelvic Floor Monthly - August Report - Next Gen Materials Progress

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Dear Giselle (and Steve),

(SENSITIVE AND CONFIDENTIAL INFORMATION - Please do not share with anyone without discussing with me first)
Ronnie, Gene and I have had several meetings with CBAT (Center for Biomaterials and Advanced Technology group) to review their lab learnings from investigating several composite materials and therefore provide some direction for a Next Gen Pelvic Floor Material:

A) GYNEMESH PS + Bovine Collagen/Gag Matrix (Integra = Advanced Wound Care product used for Burns patients)
B) GYNEMESH PS + Proceed (Interceed + PDS - FYI this is a composite mesh released by EPD)
C) GYNEMESH PS + Europa (35% PCL, 65% PGA = CBAT material)

The key insights related to orientation of the collagen fibrils and therefore characteristics that could positively improve/reduce tissue contraction around the mesh. GYNEMESH PS today has a "swirling effect" causing what doctors have expressed as "shrinkage or contraction of the mesh". It isn't the mesh that's contracting, its the tissue that seems to be "bunching" up resulting in the desire to have a more "tension-free" fixation.
Bottom line, if you have collagen trails in ONE Direction, it is likely to cause MORE contraction.
Therefore, collagen trails that are multidirectional/more random may be BETTER to reduce contraction.

ETH.MESH.00442831:

-----Original Message-----
From: Kammerer, Gene [ETHUS]
Sent: Tuesday, January 18, 2005 11:21 AM
To: Brown, Kelly [ETHUS]
Cc: Yang, Chunlin [ETUS]; Walji, Zenobia [ETHUS]; Engel, Dr. Dieter [ETHDE]; Holste, Dr. Joerg [ETHDE]; Parisi, Paul [ETHUS]
Subject: RE: Proposal for work with CBAT

Kelly,
Are we beginning to make the samples? If so, I think we were going to do the synthetic material first then the collagen. If help is needed, I am available.

On another note, I spoke with Prof Mauro Cervigni today. He is an Italian gynecologist. He uses Gynemesh and Pelvicol to do a tension free pelvic floor repair. We talked about his requirements for an ideal mesh, what problems he is having with his current materials, and a lot about his procedure and technique. Some important points which he made:
1) infection is present in 8% of his cases and leads to erosions, therefore an antibiotic action in the mesh is needed. Erosion is present in 10% to 8% of his cases. He always sees an low grade fever associated with erosion, whether or not the infection actually is detected.
2) faster tissue repair would prevent complications of erosion and Dyspareunia, the later generally caused by scar contraction
a. contraction pulls against the side wall and causes pain
b. it causes a hard tissue which can be felt by patient and sexual partner
c. it can lead to a balling up of the mesh which is very uncomfortable
d. it can lead to suture line dehiscence
e. it can lead to prolapse recurrence

ETH-18761 (January 18, 2005):

Thank you also for your notes on the conversation with Prof. Mauro Cervigni. I find the perceived correlations between infection, mesh acceptance/tissue healing and vascularity intriguing (particularly in light of our proposed test samples that may aid vascularity). I also find the comments about mechanical property needs to be useful. I would like to learn more about UltraPro Mesh - perhaps we can include it in our battery of samples at some stage. In general, I am always pleased to learn of the commonalities in surgeons' observations. Many of the points that Prof. Cervigni mentioned have been voiced by other surgeons which gives me a degree of confidence in considering these issues in our innovative efforts.

Kelly

ETH.MESH.04945233

-----Ursprüngliche Nachricht-----
Von: Kammerer, Gene [ETHUS]
Gesendet: Mittwoch, 13. April 2005 18:27
An: Barbolt, Thomas [ETHUS]; Holste, Dr. Joerg [ETHDE]; Dormier, Edward [ETHUS]; Batke, Boris [ETHDE]
Cc: Angelini, Laura [ETHIT]; Guidry, Cyrus [ETHUS]; Schwartz, Barbara [ETHUS]; Engel, Dr. Dieter [ETHDE]; Storch, Mark L. [ETHUS]; Savidge, Sandy [ETHUS]; Brown, Kelly [ETHUS]
Betreff: RE: ULTRAPRO vs PROLENE Soft Mesh
Vertraulichkeit: Vertraulich

Tom,
Regarding which attributes to investigate to show a difference between materials, I have this input. The issue which I am trying to investigate/solve is one of scar contracture around the mesh. In pelvic floor repair even with the PSM, we have seen some scar contracture which translates into procedural complications. I don't want to state % here because the situation which produces the complication is in itself complicated and specific to each patient. Also, most of the data comes from VOC and not our documented studies. However, it is important to know that the surgeons who are our consultants on the ProLift product are asking for a mesh which is better than PSM in this area.
The complications which are identified in the market are 1) recurrence of the prolapse 2) pain 3) stiffness 4) erosion and 5) discomfort during sex. The surgeons attribute these conditions to scar contracture. If we could find a way to reduce the scar formation by some % and subsequently the contracture it would give us a significant advantage over the competition as well as make the procedure better for the patient. One way to prove this is, as you stated, by identifying the tissue reaction attributes which are directly associated with scar formation and contracture. Start with in vitro studies and then in vivo studies to show a specific link and a clear

b. Ethicon Knew about Complications and Did Not Inform Doctors How to Manage Them

ETH.MESH.02341398 (Prosima IFU)

CONTRAINDICATIONS

- When GYNECARE GYNEMESH PS is used in infants, children, pregnant women, or women planning future pregnancies, the surgeon should be aware that this product will not stretch significantly as the patient grows.
- The GYNECARE PROSIMA System should not be used in the presence of pregnancy or purulent infections or cancers of the vagina, cervix, or uterus.

WARNINGS AND PRECAUTIONS

- Users should be familiar with surgical procedures and techniques involving pelvic floor repair and nonabsorbable meshes before employing the GYNECARE PROSIMA Systems.
- Use of the GYNECARE PROSIMA System has not been fully evaluated in patients with Stage IV pelvic organ prolapse. Therefore its use in these patients is not recommended.
- Acceptable surgical practice should be followed for the GYNECARE PROSIMA System as well as for the management of infected or contaminated wounds.
- Do not use the GYNECARE PROSIMA System if you think the surgical site may be infected or contaminated. If the Mesh Implant or VSD-Balloon Assembly is used in contaminated areas it must only be with the understanding that subsequent infection may require its removal.
- Postoperatively the patient should be advised to refrain from heavy lifting and/or exercise (e.g. cycling, jogging) for 3 to 4 weeks and to refrain from sexual intercourse for 6 weeks or until the physician determines it is suitable for the patient to return to her normal activities.
- Do not leave the VSD inside the vagina for longer than 4 weeks.
- Do not leave the Balloon inside the vagina for longer than 1 day.
- The GYNECARE PROSIMA System components are not intended to be used with devices other than those mentioned in this package insert.
- Avoid placing excessive tension on the Mesh Implant during handling.
- Use the GYNECARE PROSIMA Systems with care, and with attention to patient anatomy, to avoid damage to vessels, nerves, bladder, bowel, and vaginal wall perforation. Correct use of the GYNECARE PROSIMA System components will minimize risks.
- Inflate the Balloon only with ambient air.
- Palpation will confirm that the Balloon does not contain any air leaks after inflation. Complete loss of inflation may limit the Balloon's effectiveness.
- The Balloon wall is thin in order to achieve desired properties. Punctures, cuts, nicks, crushing, or overstressing can lead to a loss of inflation. The Balloon may be easily penetrated by needle or scalpel or ruptured by manipulation with a blunt instrument. Care must be exercised during handling to prevent such events. A damaged Balloon must not be used. Remove and pack with gauze.
- The Balloon inflation maximum is 90 mL. Do not over-inflate the Balloon. Excessive inflation of the Balloon may cause patient discomfort, tissue necrosis, disruption of vaginal wound postoperatively, or inability to void.
- Do not use GYNECARE PROSIMA Systems on patients who are on anti-coagulant therapy.

- Bleeding may occur postoperatively. Observe for any symptoms or signs before releasing the patient from the hospital.
- The patient should be instructed to contact the surgeon immediately if unusual pain, bleeding, or other problems occur.
- Although bladder injury is unlikely to occur with this technique, cystoscopy is recommended to be performed.
- Although rectal injury is unlikely to occur with this technique, a digital exam is required to be performed.
- Do not affix the GYNECARE GYNEMESH PS Mesh Implant with any staples, clips, or clamps as mechanical damage to the mesh may occur.
- The Mesh Implant should not be present in the lower 1/3 of vagina. If needed, trim the Mesh Implant to the junction of the lower and middle 1/3 of vaginal wall.
- Prophylactic antibiotics can be administered according to the surgeon's usual practice.

ADVERSE REACTIONS

- Potential adverse reactions are those typically associated with surgically implantable materials, including infection potentiation, inflammation, adhesion formation, fistula formation, erosion, extrusion and scarring that result in implant contraction.
- Potential adverse reactions are those typically associated with pelvic organ prolapse repair procedures, including pain with intercourse and pelvic pain. These may be self-resolving over time.
- Punctures or lacerations or injury to vessels, nerves, bladder, urethra, or bowel may occur during dissection or mesh placement and may require surgical repair.
- Dissection for pelvic floor repair procedures has the potential to impair normal voiding for a variable length of time.

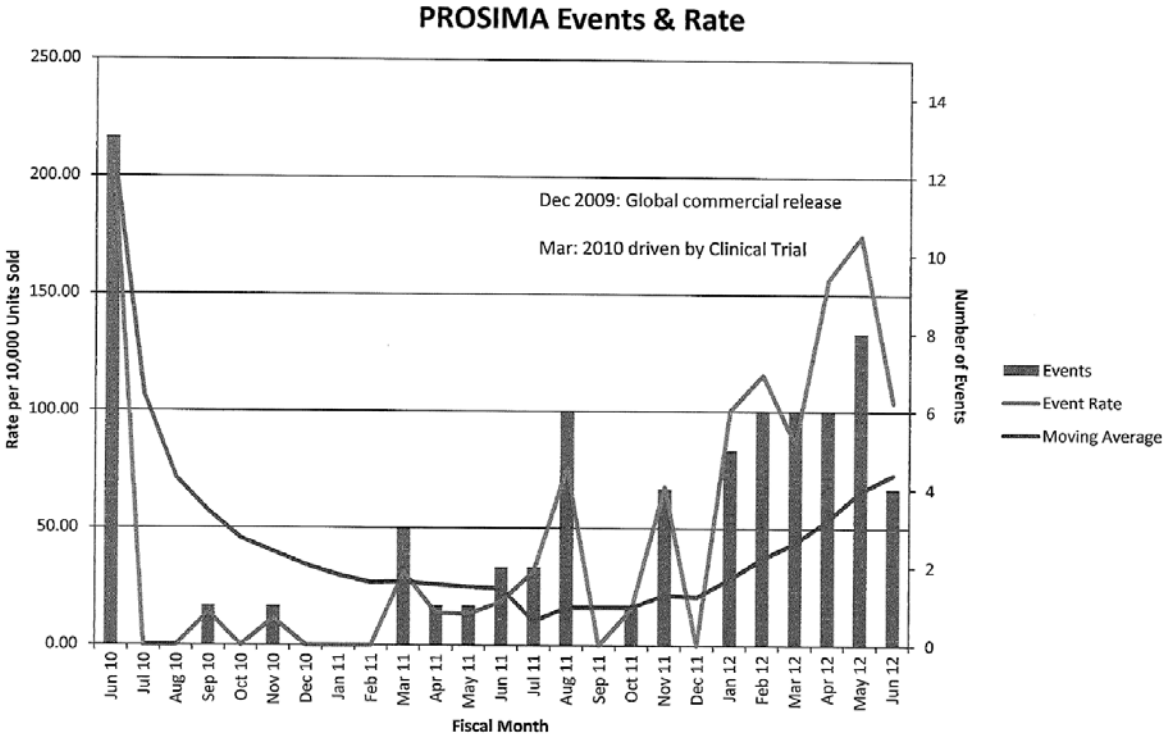
ETH.MESH.10608341

Form (Non-PPE) 100123366/Rev: 3
Quality System CO: 100107923
Franchise Form for Post Market Surveillance Reports (PMSR)

- GYNECARE PROSIMA

Complaints: All three product families that comprise the Pelvic Floor Repair System PMS Category have experienced a significant increase in reported complaints over the referenced period of this PMSR. As noted in Tables 1, 2 & 3 below, the increase in reported complaints originated in Q3 of 2011 which corresponds with the timing of an FDA Panel Session focusing on Pelvic Floor Meshes and Trans-vaginal Tapes. Bracketing the period of 1/2012 – 1/2013, PROLIFT, PROLIFT M and PROSIMA have experienced between a four to eight fold increase in reported events with a corresponding increasing event rate recorded over that same period. The most dramatic increases can be seen in the PROLIFT product family.

ETH.MESH.06773944



June 2012 WHU Complaint Review 58 CONFIDENTIAL- For Internal Use Only

ETH.MESH.06900544

12. He did not feel this would be an effective procedure for grades 3 or 4 based on his personal experience of seeing failures with this technique and said that even if the clinical study showed good results, he would be suspicious of the data.
13. Study would need to have one-year follow up to prove durability.
14. Felt that the cost of MINT should be substantially less than Prolift however he said the cost should primarily be in balanced relationship to the reimbursement.

ETH.MESH.05009194

----- Original Message -----
From: HARCOURT, Rosalyn [MEDAU]
To: Meek, Jonathan [ETHUS]
Sent: Wed Apr 23 20:45:06 2008
Subject: RE: PROLIFT + M Registration

This is via a third person rather than directly to me, basically that he feels J&J don't look after him and appreciate his status in the industry. Apparently there was a conference that he was asked to speak at on short notice and J&J wouldnt pay for his airfare as he was already going there. He feels that his feedback on products is not being listened to as a top KOL and that there are other companies chasing him, offering to look after him at a much higher level.

As to whether or not any of this is true, I don't know however I thought it should be passed on. When he went through his presentations with me he was quite scathing of PROSIMA being a reckless product, TVT Secur as having problems and being behind MINI ARC in terms of reliability. I do know that several comments were made in surgeny (off camera) about TVT Secur, the use of ULTRAPRO for gyne surgery (now there is a can of worms that we didnt need promoted).

P1704.

Prolift®: experience of the University hospital of Clermont-Ferrand

Prospective study	**Prolift®: patients operated on between March 2005 and August 2006**
Follow-up	18 months [12-27]
Patients included -available for follow-up	125 patients 107 patients
Mean age	66.7 years [42-87]
Menopause - HRT	118 patients (94.4%) 29 patients (23.2%)
Previous POP surgery	37 patients (29.6%)
Previous hysterectomy	45 patients (36%)
Previous SUI surgery	23 patients (18.4%)
Surgical procedure	**Anterior Prolift: 32.8%** **Posterior Prolift: 16%%** **Total or Ant+Post Prolift: 51.2% (20.1% + 31.2%)**
Mesh exposure rate - 3 months - max f/u	**11.2%** **14%**
Painful mesh shrinkage	**19.6%**
Global objective success rate	**75.7%** **POPQ<2 (-1cm)**

P.1704, p.23

Functional results : painful mesh shrinkage

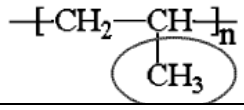
- Painful mesh shrinkage (at vaginal examination)
  - 21 patients (19.6%)
    - 13 sexually active
      - 5 without dyspareunia
      - 2 dyspareunie “often” (VAS 5 and 8 respectively)
      - 3 dyspreunia “sometimes” (VAS 5)
      - 3 didn’t complete the questionnaire
    - 8 sexually inactive
      - 1 became sexually inactive because of dyspareunia

Correlation between painful mesh shrinkage and dyspareunia but not systematic

ETH.MESH.02589066

Polypropylene can suffer from degradation following implant

- Polypropylene has a long history of use but it is subject to degradation; a process which initiates after a few days post implantation in animal studies[1]
  - This study proposes oxidation as the degradation mechanism, reporting that polypropylene filaments containing an antioxidant were less susceptible to oxidation
  - Oxidation usually occurs at the tertiary repeating position in the polymer, where a free radical is formed that then reacts with oxygen, followed by chain scission to produce aldehydes and carboxylic acids. In external applications, it shows up as a network of fine cracks that become deeper and more severe with time of exposure
  - Degradation of polypropylene has also been reported in the eye, where sutures were used to implant an intraocular lens[2] ; the authors suggest enzymatic degradation
  - Macrophages excrete acidic compounds that can initiate oxidation processes[4]
  - One clinician interviewed proposed that variability in the raw materials, and/or processing thereof, could be affecting the clinical performance and outcomes. He articulated his intention to investigate this hypothesis
  - High resolution images[3] of excised meshes clearly show physical degradation of polypropylene filaments



ETH.MESH.00870466

Ethicon Expert Meeting
Meshes for Pelvic Floor Repair
Friday, June 2, 2006; Location: Oststr. 1, Norderstedt, Meeting Room "Forum"

Vaginal pain after implantation of meshes is rare, but feared, since there is not real treatment option (V. Lucente: prefer 20 recurrences or Erosions over 1 pain patient)

ETH.MESH.00870466

Biological response to surgical mesh (Prof. Klosterhalfen)
Huge surface area of meshes (e.g. more than 300 m of suture)
Even after 20 years the tissue is still reacting to the mesh.
Fibrosis is responsible for complications in mesh usage. ' Redacted
compared to PP
Foreign body reaction:

- Fibrinogen and Albumin bind to biomaterial, change and activate the immunologic syster
- active process, a "chronic wound", to be demonstrated by proliferating and dying cells
- combination of material and genetics.

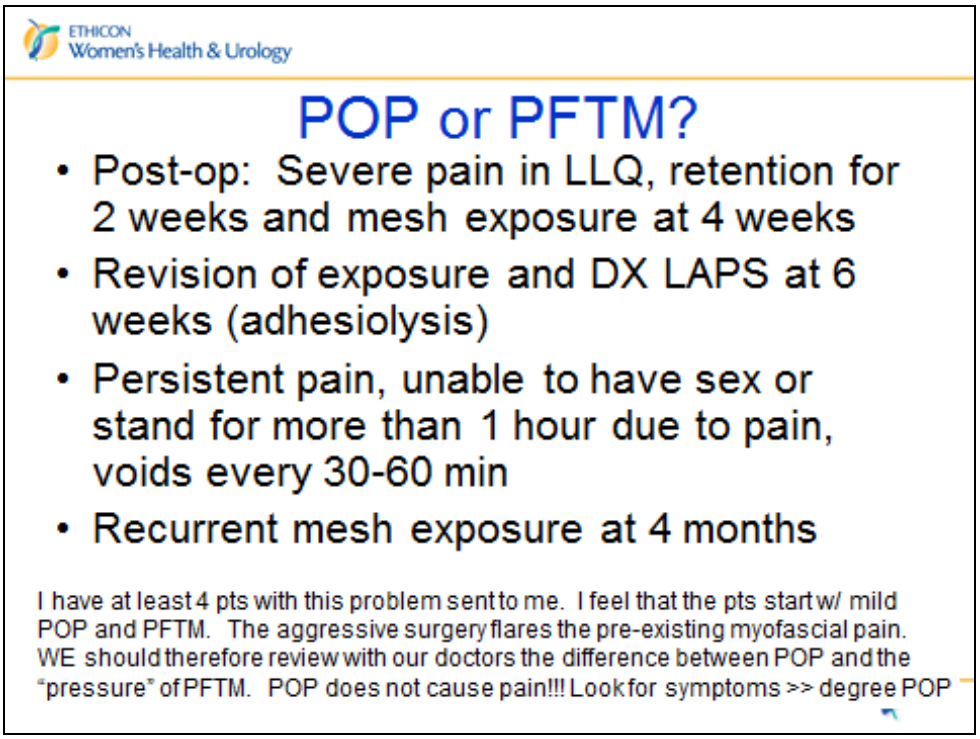
Optimum pore size is material dependent (critical pores size; at least 1-2mm), scar formation a combination of pore size, surface area, polymer.
Large pores: fibrosis on the mesh fiber only
Small pores: interconnection between mesh pores due to fibroses leading to mesh shrinkage.

Shrinkage of 20% means reduction of mesh area to 64%

Tension of the mesh changes pore size → change in elasticity
Films or Foils cause more shrinkage than meshes
Meshes can cause Nerve damage due to mechanical irritation (mesh bears on nerve)
There is no inert material

Unmet clinical needs	**Priority (points)**
No shrinkage / no long-term contraction Fibrosis reduction Severe contraction → Dyspareunia → sexual function ↓ *Tension response ↓* = ↓ *Sexual pain?* *No folding of mesh* *No rigidity*	10
No vaginal distortion, normal vaginal wall, maintain sexual function, normal sexual function	8

ETH.MESH.02289896



P1706 (June 2009)

Conclusion

Mesh shrinkage

- Is real !
- Occurs during the scarring and remodelling process
- May result in a unpredictable way in severe complications including dyspareunia, pain and recurrence
- May require mesh removal
- Must be taken into consideration during patient councelling before surgery

Is a challenge for the next years !

⇒ Need for a better understanding
⇒ Need for a better assessment
⇒ Need for a better material behaviour (and techniques)

ETH.MESH.03923931 (Press Interview, Frankfort, June 9, 2005)

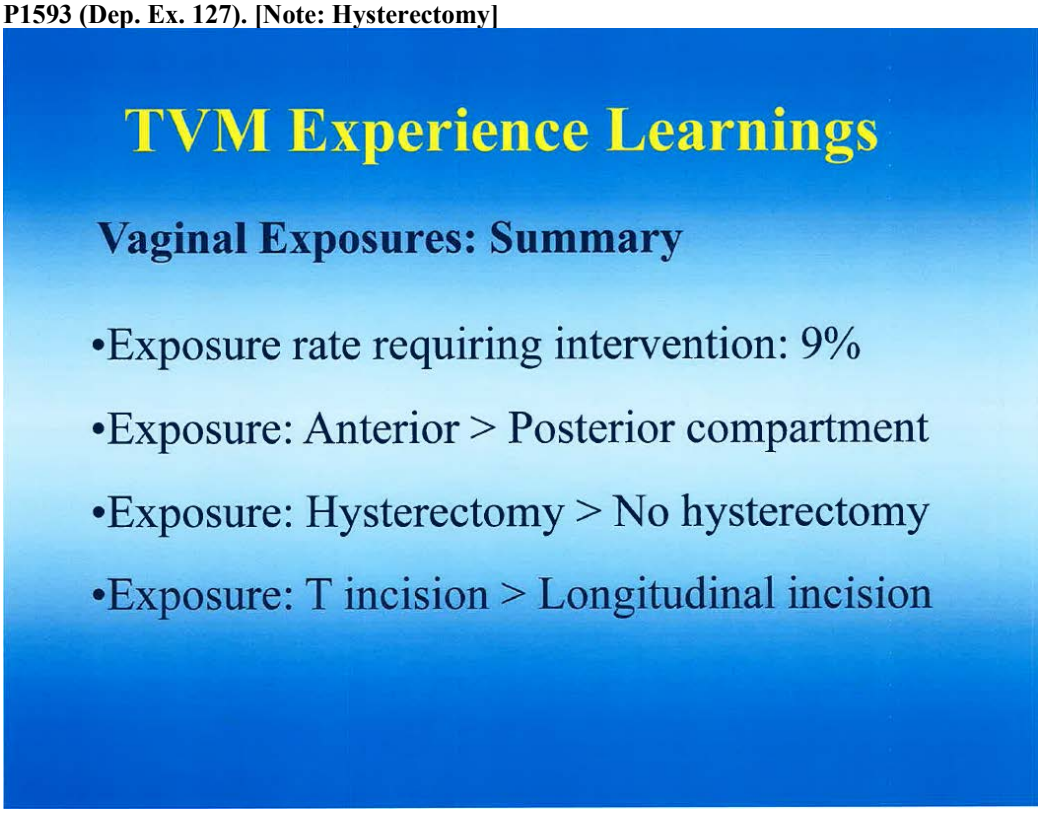
Comments

1. Mesh exposure is usually a minor complication. It can get cured most of the time by a simple excision of the part of the mesh that is apparent and a new vaginal closure.
Interestingly, the preliminary experience led to the identification of two key factors for the formation of an exposure:

- a concomitant hysterectomy:
- longitudinal incisions in the vagina.

Logically, the Group decided to change the type of the vaginal incisions and challenged the need for a systematic hysterectomy during prolapse surgery. This led to a dramatic decrease of the mesh exposure rate (<1%) when hysterectomy was not performed.
2. Shrinkage is due to an excessive scarring process. Even if most of the time it is asymptomatic, in a few cases it led to vaginal distortion impacting the sexual life. Thus, the procedure must be used cautiously in sexually active women.

P1593 (Dep. Ex. 127). [Note: Hysterectomy]



T-3321 (ETH.MESH.04082973) (Dep. of Meng Chen, MD, PhD)

Long term post-operative:

Persistent vaginal discharge (4.7%)
Vaginal bleeding (1.6%)
Dyspareunia (6.3%)
Sexual dysfunction
Recurrent prolapse (2.5%)
Mesh erosion (8.2%)
Obstructive voiding complications (11.0-18.3%)

Predictive Risk Factors for CV and Pulmonary Complications

- Age over 40
- Smoking history
- Obesity
- The presence of varicose veins

Other factors to consider

- Age
- Weight
- Parity
- Menopause status
- Estrogen therapy
- Previous surgeries
- Degree of pre-operative prolapse

c. Ethicon Did Not Perform Clinical Trials

ETH.MESH.03915790 (continued)

I am a bit frightened to see that we are currently building a full business story on that, not having yet validated the proof of concept, neither from animal experiments nor from clinical use.
In my opinion, a logical way to proceed would be 1) to ask Deprest, for example, to compare Lightning and Gynemesh in animals and tell us if the theoretical assumption of less shrinkage is likely to be true 2) if this would be the case, we could then move on to clinicals and perform an observational study to confirm the benefits in humans 3) we could then discuss the need for a formal RCT to compare the two meshes and generate evidence that Lightning is a better choice than Gynemesh.
Alternatively, we could skip 1) and move directly to 2). If we ended up with results that would look better or at least equal to Gynemesh, we could certainly introduce the product on the market with a good chance of success (if reasonably priced) since the concept of light mesh is appealing on a surgical standpoint. If we are successful on the market, it is very unlikely that we will need to set up any RCT.
Finally, we could skip 1) and 2) and go directly for a comparative study. I do not believe this would be the best option, as it seems to me it would be expensive, long and risky.
To summarize, I support the idea of a single arm observational study.

P.1659 (Characteristics of Synthetic Materials Used in Prolapse . . . Surgery)

It is a challenging task to try to define the ideal material for pelvic floor surgery. Indeed, the scientific knowledge about the use of meshes in surgery is still in its infancy, at least for pelvic floor applications. There are far more products available on the market than randomized comparative trials which could help making a clear distinction among them.

In the absence of strong clinical evidence, one have to rely on various sources to try to help the surgeons to make an appropriate choice when considering the use of a synthetic material. These are essentially: basic knowledge from the science of textiles, clinical and fundamental research from hernia surgery and results of the more recent clinical experience in pelvic floor reconstruction.

Thus, all the recommendations that might be given in this presentation must be viewed with respect to these difficulties of finding hard data. They should certainly be reconsidered on a regular basis as long as more evidence is made available by the searchers.

ETH.MESH.02999594

Preclinical Efficacy Support of PROSIMA*

- Challenge – No direct animal model
  - Cadaver work to support placement/deployment
  - Partner with Performance Evaluation
  - Reliance on historical use of mesh in pelvic floor repair for *some* claims

Preclinical Safety Support of PROSIMA*

Challenge – multi-component device with different patient contact categories and durations

- Predicate components – little to no testing required
  - Mesh – GYNEMESH (ultrasonic cutting, welding)
  - Inserters – polycarbonate, surgical grade stainless steel
- Novel components – testing and equivalence work
  - Vaginal support device – 30 day vaginal implant study
  - Balloon assembly – skin vs breached surface testing levels

ETH.MESH.03912703

Prosima

1. Team Update

1.1 AA informed the team about the **disappointing results of the Carey-Slack's observational study** which was considered as very important for the future launch.

A draft manuscript was received from M. Carey (Cf. Clinical Dashboard). The study involves 95 patients and apparently reports excellent results:

- objective success rate was 92 and 86% at 6 and 12 months
- subjective success rate was 91 and 86% at 6 and 12 months. Two of 4 mesh required surgery.

Nevertheless, when looking closer at the results, it appears that there is a high rate of patients lost to follow-up at the 6 months review (78/95) as well as at the 12 month review (73/95). If the results are expressed in an intention-to-treat basis, there are far less favorable.

In addition, it is uneasy to understand from the Methods section which kind of colporrhaphy was used together with the mesh repair.

ETH.MESH.03162936

Hi Both

Before we go back to Marcus, please can we three discuss this further on Monday morning - or sooner if wanted / needed.

We did state in the protocol that the study would be considered a success if the failure rate had an upper 95% CI of less than 20% at 12 months. We have already failed that. I am concerned here that this looks like a good bit of spin going on, and due to his commercial interest, this is not going to come over as objective as perhaps it should. Whilst this type of message might be great once we've identified the problems, and are presenting to preceptors, etc, I'm not sure that it would be well placed in this meeting.

I'd been planning to pull together all the findings from the publications Marcus mentions below, but more (mesh ones) in our slides so we could objectively assess what's already out there. We can't get away from the fact that there will be comparisons made to Prolift and other mesh systems. Therefore, to this audience (investigators) we need to be completely objective and be prepared to discuss all previous research in the area. Whilst Marcus refers to ASC as the "gold-standard" alot of our investigator may consider "Prolift" the vaginal "gold-standard" (due to their experience rather than based on evidence), and many of them will want to discuss how it compares.

Let me know what you think.

Judi

ADDITIONAL DISCLOSURES

I may be asked to review additional materials and/or documentation as the case progresses and, in that event, I reserve the right to supplement this report. My current hourly fee is $650/hour, not including testimony.

During the previous four years, I have testified as an expert witness at deposition or trial in the following cases:

In re: C.R. Bard, Inc. Pelvic Repair Sys. Prods. Liab. Litig., MDL No. 2187 (S.D. W.Va.)
Nava v. Boston Scientific Corp., et al., Civ. Action No. 2:13-cv-14455 (S.D. W.Va.)
In re: Boston Scientific Corp., MDL No. 2326 (S.D. W. Va.)
Callen v. C.R. Bard, Inc., Civ. Action No. 2:14-CV-14375 (S.D. W. Va.)
Harrison v. C.R. Bard, Inc., Civ. Action No. 2:12-CV-06602 (S.D. W. Va.)
Huber v. C.R. Bard, Inc., Civ. Action No. 2:13-CV-02424 (S.D. W. Va.)
Jay v. C.R. Bard, Inc., Civ. Action No. 2:13-CV-08536 (S.D. W. Va.)
Rueda v. C.R. Bard, Inc., Civ. Action No. 2:13-CV-02175 (S.D. W. Va.)
Smitty v. C.R. Bard, Inc., Civ. Action No. 2:13-cv-33750 (S.D. W. Va.)

This 1st day of February, 2016.

Bob Shull MD

Bob Shull MD